



General

Guideline Title

2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines.

Bibliographic Source(s)

Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC Jr, Watson K, Wilson PW. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014 Jul 1;63(25 Pt B):2889-934. [144 references] [PubMed](#)

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Note from the National Guideline Clearinghouse (NGC): National Heart, Lung and Blood Institute (NHLBI) Evidence Statements are also included for each recommendation. See Appendix 4 in the original guideline document.

Each recommendation has been mapped from the NHLBI grading format to the American College of Cardiology/American Heart Association Class of Recommendation/Level of Evidence (ACC/AHA COR/LOE) construct and is expressed in both formats. Because of the inherent differences in grading systems and the clinical questions driving the recommendations, alignment between the NHLBI and ACC/AHA formats is in some cases imperfect. Definitions for the NHLBI strength of recommendation (A-E, N) and quality of evidence (High, Moderate, Low) and the ACC/AHA levels of the evidence (LOE: A-C) and classes of recommendations (COR: I-III) are provided at the end of the "Major Recommendations" field.

What's New in the Guideline?

Focus on Atherosclerotic Cardiovascular Disease (ASCVD Risk) Reduction: 4 Statin Benefit Groups

1. This guideline is based on a comprehensive set of data from randomized control trials (RCTs) from which 4 statin benefit groups were identified that focus efforts to reduce ASCVD events in secondary and primary prevention.

2. This guideline identifies high-intensity and moderate-intensity statin therapy for use in secondary and primary prevention.

A New Perspective on Low-density Lipoprotein Cholesterol (LDL-C) and/or Non-High-density Lipoprotein Cholesterol (HDL-C) Treatment Goals

1. The Expert Panel was unable to find RCT evidence to support continued use of specific LDL-C or non-HDL-C treatment targets.
2. The appropriate intensity of statin therapy should be used to reduce ASCVD risk in those most likely to benefit.
3. Nonstatin therapies, as compared with statin therapy, do not provide acceptable ASCVD risk-reduction benefits relative to their potential for adverse effects in the routine prevention of ASCVD.

Global Risk Assessment for Primary Prevention

1. This guideline recommends use of the new Pooled Cohort Equations to estimate 10-year ASCVD risk in both white and black men and women.
2. By more accurately identifying higher-risk individuals for statin therapy, the guideline focuses statin therapy on *those most likely to benefit*.
3. It also indicates, on the basis of RCT data, those high-risk groups that might not benefit.
4. This guideline recommends a discussion between clinicians and patients before initiation of statin therapy.

Safety Recommendations

1. This guideline used RCTs to identify important safety considerations in individuals receiving treatment of blood cholesterol to reduce ASCVD risk.
2. Using RCTs to determine statin adverse effects facilitates understanding of the net benefit from statin therapy.
3. This guideline provides expert guidance on management of statin-associated adverse effects, including muscle symptoms.

Role of Biomarkers and Noninvasive Tests

1. Treatment decisions in selected individuals who are not included in the 4 statin benefit groups may be informed by other factors as recommended by the Risk Assessment Work Group and Blood Cholesterol Expert Panel.

Future Updates to the Blood Cholesterol Guideline

1. This is a comprehensive guideline for the evidence-based treatment of blood cholesterol to reduce ASCVD risk.
2. Future updates will build on this foundation to provide expert guidance on the management of complex lipid disorders and incorporate refinements in risk stratification based on critical review of emerging data.
3. RCTs comparing alternative treatment strategies are needed in order to inform future evidence-based guidelines for the optimum ASCVD risk-reduction approach.

Note: See Appendix 5 in the original guideline document for an expanded discussion of what's new in the guideline.

Recommendations for Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults—Statin Treatment

Treatment Targets

1. The Expert Panel makes no recommendations for or against specific LDL-C or non-HDL-C targets for the primary or secondary prevention of ASCVD. NHLBI Grade: N (No recommendation); ACC/AHA COR: n/a; ACC/AHA LOE: n/a

Secondary Prevention

1. High-intensity statin therapy should be initiated or continued as first-line therapy in women and men ≤ 75 years of age who have *clinical ASCVD**, unless contraindicated. NHLBI Grade: A (Strong); ACC/AHA COR: I; ACC/AHA LOE: A
2. In individuals with *clinical ASCVD** in whom high-intensity statin therapy would otherwise be used, when high-intensity statin therapy is contraindicated† or when characteristics predisposing to statin-associated adverse effects are present, moderate-intensity statin should be used as the second option if tolerated (see "Safety of Statins," below). NHLBI Grade: A (Strong); ACC/AHA COR: I; ACC/AHA LOE: A

3. In individuals with *clinical ASCVD* >75 years of age, it is reasonable to evaluate the potential for ASCVD risk-reduction benefits and for adverse effects and drug–drug interactions and to consider patient preferences when initiating a moderate- or high-intensity statin. It is reasonable to continue statin therapy in those who are tolerating it. NHLBI Grade: E (Expert Opinion); ACC/AHA COR: IIa; ACC/AHA LOE: B (Heart Protection Study Collaborative Group, 2002; Cholesterol Treatment Trialists' [CTT] Collaboration et al., 2010; Tikkanen et al., 2009; Holmes et al., 2006; Akushevich et al., 2012; Wolff, Starfield & Anderson, 2002; Fried et al., "Effects," 2011; Robinson et al., 2007; Porock et al., 2005; Stineman et al., 2012; Schonberg et al., 2011; Fried et al., "Health outcome," 2011; Barry & Edgman-Levitan, 2012; Man-Son-Hing, Gage, & Montgomery, 2005; Fried et al., 2002; Ditto et al., 1996; Rosenfeld, Wenger, & Kagawa-Singer, 2000; Nease et al., 1995; Glynn et al., 2010; Shepherd et al., 2002; Trompet et al., 2010; Gray et al., 2011; LaCroix et al., 2008; Hippisley-Cox et al., 2005; Forman et al., 2011)

Primary Prevention in Individuals ≥ 21 Years of Age with LDL-C ≥ 190 mg/dL

1. Individuals with LDL-C ≥ 190 mg/dL or triglycerides ≥ 500 mg/dL should be evaluated for secondary causes of hyperlipidemia (see Table 6 in the original guideline document). NHLBI Grade: B (Moderate); ACC/AHA COR: I \ddagger ; ACC/AHA LOE: B (Berglund et al., 2012; Miller et al., 2011)

2. Adults ≥ 21 years of age with primary LDL-C ≥ 190 mg/dL should be treated with statin therapy (10-year ASCVD risk estimation is not required) NHLBI Grade: B (Moderate); ACC/AHA COR: I \S ; ACC/AHA LOE: B:

- Use high-intensity statin therapy unless contraindicated.
- For individuals unable to tolerate high-intensity statin therapy, use the maximum tolerated statin intensity.

3. For individuals ≥ 21 years of age with an untreated primary LDL-C ≥ 190 mg/dL, it is reasonable to intensify statin therapy to achieve at least a 50% LDL-C reduction. NHLBI Grade: E (Expert Opinion); ACC/AHA COR: IIa; ACC/AHA LOE: B (CTT Collaboration et al., 2010; LaRosa et al., 2005; Pedersen et al., 2005; Cannon et al., 2004; Ridker et al., 2008; Baigent et al., 2005)

4. For individuals ≥ 21 years of age with an untreated primary LDL-C ≥ 190 mg/dL, after the maximum intensity of statin therapy has been achieved, addition of a nonstatin drug may be considered to further lower LDL-C. Evaluate the potential for ASCVD risk-reduction benefits, adverse effects, and drug–drug interactions, and consider patient preferences. NHLBI Grade: E (Expert Opinion); ACC/AHA COR: IIb; ACC/AHA LOE: C (Thompson, Packard, & Stone, 2004)

Primary Prevention in Individuals with Diabetes and LDL-C 70–189 mg/dL

1. Moderate-intensity statin therapy should be initiated or continued for adults 40 to 75 years of age with diabetes. NHLBI Grade: A (Strong); ACC/AHA COR: I; ACC/AHA LOE: A

2. High-intensity statin therapy is reasonable for adults 40 to 75 years of age with diabetes with a $\geq 7.5\%$ estimated 10-year ASCVD risk—unless contraindicated. NHLBI Grade: E (Expert Opinion); ACC/AHA COR: IIa; ACC/AHA LOE: B (Ridker et al., 2008; Ridker et al., 2012)

3. In adults with diabetes, who are <40 years of age or >75 years of age, or with LDL <70 mg/dL, it is reasonable to evaluate the potential for ASCVD benefits and for adverse effects and drug–drug interactions and to consider patient preferences when deciding to initiate, continue, or intensify statin therapy. NHLBI Grade: E (Expert Opinion); ACC/AHA COR: IIa; ACC/AHA LOE: C (Roffi, Angiolillo, & Kappetein, 2011; Nathan et al., 2005; Rhodes et al., 2012; Paynter et al., 2011; Elley et al., 2010; Stevens et al., 2004; Bibbins-Domingo et al., 2007; Daniels et al., 2009; Jacob & Cho, 2010; Bainey & Jugdutt, 2009)

Primary Prevention in Individuals without Diabetes and with LDL-C 70–189 mg/dL

1. The Pooled Cohort Equations should be used to estimate 10-year ASCVD—risk for individuals with LDL-C 70–189 mg/dL without *clinical ASCVD** to guide initiation of statin therapy for the primary prevention of ASCVD. NHLBI Grade: E (Expert Opinion); ACC/AHA COR: I; ACC/AHA LOE: B (Goff et al., 2014)

2. Adults 40 to 75 years of age with LDL-C 70–189 mg/dL, without *clinical ASCVD** or diabetes, and with an estimated 10-year ASCVD—risk $\geq 7.5\%$ should be treated with moderate- to high-intensity statin therapy. NHLBI Grade: A (Strong); ACC/AHA COR: I; ACC/AHA LOE: A

3. It is reasonable to offer treatment with a moderate-intensity statin to adults 40 to 75 years of age, with LDL-C 70–189 mg/dL, without *clinical ASCVD** or diabetes, and with an estimated 10-year ASCVD—risk of 5% to <7.5%. NHLBI Grade: C (Weak); ACC/AHA COR: IIa; ACC/AHA LOE: B

4. Before initiation of statin therapy for the primary prevention of ASCVD in adults with LDL-C 70–189 mg/dL without *clinical ASCVD** or diabetes, it is reasonable for clinicians and patients to engage in a discussion that considers the potential for ASCVD risk-reduction benefits and for adverse effects and drug–drug interactions, as well as patient preferences for treatment. NHLBI Grade: E (Expert Opinion); ACC/AHA COR:

5. In adults with LDL-C <190 mg/dL who are not otherwise identified in a statin benefit group, or for whom after quantitative risk assessment a risk-based treatment decision is uncertain, additional factors¶ may be considered to inform treatment decision making. In these individuals, statin therapy for primary prevention may be considered after evaluation of the potential for ASCVD risk-reduction benefits, adverse effects, and drug–drug interactions and consider patient preferences. NHBLI Grade: E (Expert Opinion); ACC/AHA COR: IIb; ACC/AHA LOE: C (Goff et al., 2014; CTT Collaborators et al., 2012)

Heart Failure and Hemodialysis

1. The Expert Panel makes no recommendations regarding the initiation or discontinuation of statins in patients with NYHA class II–IV ischemic systolic heart failure or in patients on maintenance hemodialysis. NHBLI Grade: N (No Recommendation); ACC/AHA COR: n/a; ACC/AHA LOE: n/a

*Clinical ASCVD includes acute coronary syndromes, history of myocardial infarction (MI), stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischaemic attack (TIA), or peripheral arterial disease presumed to be of atherosclerotic origin.

†Contraindications, warnings, and precautions are defined for each statin according to the manufacturer's prescribing information ("Lescol," 2012; "Pravachol," 2012; "Livalo," 2012; "Zocor," 2012; "Mevacor," 2012; "Lipitor," 2012; "Crestor," 2013).

‡Individuals with secondary causes of hyperlipidemia were excluded from RCTs reviewed. A triglyceride level ≥500 mg/dL was an exclusion criterion for almost all RCTs. Therefore, ruling out secondary causes is necessary to avoid inappropriate statin therapy.

§No RCTs included only individuals with LDL-C ≥190 mg/dL. However, many trials did include individuals with LDL-C ≥190 mg/dL, and all of these trials consistently demonstrated a reduction in ASCVD events. In addition, the Cholesterol Treatment Trialists meta-analyses have shown that each 39-mg/dL reduction in LDL-C with statin therapy reduced ASCVD events by 22%, and the relative reductions in ASCVD events were consistent across the range of LDL-C levels. Therefore, individuals with primary LDL-C ≥190 mg/dL should be treated with statin therapy.

ÇEstimated 10-year or "hard" ASCVD risk includes first occurrence of nonfatal MI, coronary heart disease death, and nonfatal and fatal stroke as used by the Risk Assessment Work Group in developing the Pooled Cohort Equations.

¶These factors may include primary LDL-C ≥160 mg/dL or other evidence of genetic hyperlipidemias; family history of premature ASCVD with onset <55 years of age in a first-degree male relative or <65 years of age in a first-degree female relative; high-sensitivity C-reactive protein ≥2 mg/L; coronary artery calcium (CAC) score ≥300 Agatston units or ≥75th percentile for age, sex, and ethnicity (for additional information, see <http://www.mesa-nhlbi.org/CACReference.aspx> [redacted]); ankle-brachial index (ABI) <0.9; or lifetime risk of ASCVD. Additional factors that might aid in individual risk assessment could be identified in the future.

See Table 5 in the original guideline document for high-, moderate-, and low-intensity statin therapies used in the RCTs reviewed by the Expert Panel.

Statin Safety Recommendations

Safety

1. To maximize the safety of statins, selection of the appropriate statin and dose in men and nonpregnant/nonnursing women should be based on patient characteristics, level of ASCVD* risk, and potential for adverse effects. Moderate-intensity statin therapy should be used in individuals in whom high-intensity statin therapy would otherwise be recommended when characteristics predisposing them to statin-associated adverse effects are present. Characteristics predisposing individuals to statin adverse effects include but are not limited to: NHBLI Grade: A (Strong); ACC/AHA COR: I; ACC/AHA LOE: B

- Multiple or serious comorbidities, including impaired renal or hepatic function
- History of previous statin intolerance or muscle disorders
- Unexplained alanine aminotransferase (ALT) elevations ≥3 times the upper limit of normal (ULN)
- Patient characteristics or concomitant use of drugs affecting statin metabolism
- Age >75 years

Additional characteristics that could modify the decision to use higher statin intensities might include but are not limited to:

- History of hemorrhagic stroke
- Asian ancestry

2a. Creatine kinase (CK) should not be routinely measured in individuals receiving statin therapy. NHBLI Grade: A (Strong); ACC/AHA COR: III: No Benefit; ACC/AHA LOE: A

2b. Baseline measurement of CK is reasonable for individuals believed to be at increased risk for adverse muscle events because of a personal or family history of statin intolerance or muscle disease, clinical presentation, or concomitant drug therapy that might increase the risk of myopathy. NHBLI Grade: E (Expert Opinion); ACC/AHA COR: IIa; ACC/AHA LOE: C (Eckel, 2010)

2c. During statin therapy, it is reasonable to measure CK in individuals with muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or generalized fatigue. NHBLI Grade: E (Expert Opinion); ACC/AHA COR: IIa; ACC/AHA LOE: C (Eckel, 2010)

3a. Baseline measurement of hepatic transaminase levels (ALT) should be performed before initiation of statin therapy. NHBLI Grade: B (Moderate); ACC/AHA COR: I†; ACC/AHA LOE: B

3b. During statin therapy, it is reasonable to measure hepatic function if symptoms suggesting hepatotoxicity arise (e.g., unusual fatigue or weakness, loss of appetite, abdominal pain, dark-colored urine, or yellowing of the skin or sclera). NHBLI Grade: E (Expert Opinion); ACC/AHA COR: IIa; ACC/AHA LOE: C (U.S. Food and Drug Administration, 2012)

4. Decreasing the statin dose may be considered when 2 consecutive values of LDL-C levels are <40 mg/dL. NHBLI Grade: C (Weak); ACC/AHA COR: IIb; ACC/AHA LOE: C

5. It may be harmful to initiate simvastatin at 80 mg daily or increase the dose of simvastatin to 80 mg daily. NHBLI Grade: B (Moderate); ACC/AHA COR: III: Harm; ACC/AHA LOE: A ("Zocor," 2012; U.S. Food and Drug Administration, 2010)

6. Individuals receiving statin therapy should be evaluated for new-onset diabetes according to the current diabetes screening guidelines (American Diabetes Association, 2013). Those who develop diabetes during statin therapy should be encouraged to adhere to a heart-healthy dietary pattern, engage in physical activity, achieve and maintain a healthy body weight, cease tobacco use, and continue statin therapy to reduce their risk of ASCVD events. NHBLI Grade: B (Moderate); ACC/AHA COR: I†; ACC/AHA LOE: B

7. For individuals taking any dose of statins, it is reasonable to use caution in individuals >75 years of age, as well as in individuals who are taking concomitant medications that alter drug metabolism, taking multiple drugs, or taking drugs for conditions that require complex medication regimens (e.g., those who have undergone solid organ transplantation or are receiving treatment for human immunodeficiency virus [HIV]). A review of the manufacturer's prescribing information may be useful before initiation of any cholesterol-lowering drug. NHBLI Grade: E (Expert Opinion); ACC/AHA COR: IIa; ACC/AHA LOE: C (Heart Protection Study Collaborative Group, 2002; "Lescol," 2012; "Pravachol," 2012; "Livalo," 2012; "Zocor," 2012; "Mevacor," 2012; "Lipitor," 2012; "Crestor," 2013; U.S. Food and Drug Administration, 2012; Rawlins, 2008; Schwartz et al., 2001; Shepherd et al., 2006)

8. It is reasonable to evaluate and treat muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or fatigue, in statin-treated patients according to the following management algorithm: NHBLI Grade: E (Expert Opinion); ACC/AHA COR: IIa; ACC/AHA LOE: B (Taylor et al., 2011; Eckel, 2010; Baigent et al., 2010; Mills et al., 2008; Dale et al., 2007)

- To avoid unnecessary discontinuation of statins, obtain a history of prior or current muscle symptoms to establish a baseline before initiation of statin therapy.
- If unexplained *severe* muscle symptoms or fatigue develop during statin therapy, promptly discontinue the statin and address the possibility of rhabdomyolysis by evaluating CK and creatinine and performing urinalysis for myoglobinuria.
- If *mild to moderate* muscle symptoms develop during statin therapy:
 - Discontinue the statin until the symptoms can be evaluated.
 - Evaluate the patient for other conditions that might increase the risk for muscle symptoms (e.g., hypothyroidism, reduced renal or hepatic function, rheumatologic disorders such as polymyalgia rheumatica, steroid myopathy, vitamin D deficiency, or primary muscle diseases).
 - If muscle symptoms resolve, and if no contraindication exists, give the patient the original or a lower dose of the same statin to establish a causal relationship between the muscle symptoms and statin therapy.
 - If a causal relationship exists, discontinue the original statin. Once muscle symptoms resolve, use a low dose of a different statin.
 - Once a low dose of a statin is tolerated, gradually increase the dose as tolerated.
 - If, after 2 months without statin treatment, muscle symptoms or elevated CK levels do not resolve completely, consider other causes of muscle symptoms listed above.
 - If persistent muscle symptoms are determined to arise from a condition unrelated to statin therapy, or if the predisposing condition has been treated, resume statin therapy at the original dose.

9. For individuals presenting with a confusional state or memory impairment while on statin therapy, it may be reasonable to evaluate the patient for nonstatin causes, such as exposure to other drugs, as well as for systemic and neuropsychiatric causes, in addition to the possibility of adverse effects associated with statin drug therapy. NHLBI Grade: E (Expert Opinion); ACC/AHA COR: IIb; ACC/AHA LOE: C (Shepherd et al., 2002; U.S. Food and Drug Administration, 2012; Collins et al., 2004; Roberts, 2009)

*Based on the presence of clinical ASCVD, diabetes, LDL-C ≥ 190 mg/dL, or level of estimated 10-year ASCVD risk.

†Individuals with elevated ALT levels (usually >1.5 or 2 times ULN) were excluded from RCT participation. Unexplained ALT ≥ 3 times ULN is a contraindication to statin therapy as listed in manufacturer's prescribing information.

‡Statin use is associated with a very modest excess risk of new-onset diabetes in RCTs and meta-analyses of RCTs (i.e., ~ 0.1 excess cases per 100 individuals treated for 1 year with moderate-intensity statin therapy and ~ 0.3 excess cases per 100 individuals treated for 1 year with high-intensity statin therapy. The increased risk of new-onset diabetes appears to be confined to those with risk factors for diabetes. These individuals are also at higher risk of ASCVD because of these risk factors. Therefore, if a statin-treated individual develops diabetes as detected by current diabetes screening guidelines, he or she should be counseled to adhere to a heart-healthy dietary pattern, engage in physical activity, achieve and maintain a healthy body weight, cease tobacco use, and continue statin therapy to reduce the risk of ASCVD events.

Nonstatin Safety Recommendations

Safety of Niacin

1. Baseline hepatic transaminases, fasting blood glucose or hemoglobin A1c, and uric acid should be obtained before initiation of niacin, and again during up-titration to a maintenance dose and every 6 months thereafter. NHLBI Grade: B (Moderate); ACC/AHA COR: I; ACC/AHA LOE: B

2. Niacin should not be used if

- Hepatic transaminase elevations are higher than 2 to 3 times ULN. NHLBI Grade: A (Strong); ACC/AHA COR: III: Harm; ACC/AHA LOE: B
- Persistent severe cutaneous symptoms, persistent hyperglycemia, acute gout, or unexplained abdominal pain or gastrointestinal symptoms occur. NHLBI Grade: B (Moderate); ACC/AHA COR: III: Harm; ACC/AHA LOE: B
- New-onset atrial fibrillation or weight loss occurs. NHLBI Grade: C (Weak); ACC/AHA COR: III: Harm; ACC/AHA LOE: B

3. In individuals with adverse effects from niacin, the potential for ASCVD benefits and the potential for adverse effects should be reconsidered before reinitiation of niacin therapy. NHLBI Grade: E (Expert Opinion); ACC/AHA COR: I; ACC/AHA LOE: B (AIM-HIGH Investigators et al., 2011; "Clofibrate and niacin in coronary heart disease," 1975; Guyton & Bays, 2007; Brown & Zhao, 2008; Grundy et al., 2002)

4. To reduce the frequency and severity of adverse cutaneous symptoms, it is reasonable to: NHLBI Grade: E (Expert Opinion); ACC/AHA COR: IIa; ACC/AHA LOE: C (AIM-HIGH Investigators et al., 2011; "Clofibrate and niacin in coronary heart disease," 1975; Guyton & Bays, 2007; Brown & Zhao, 2008; Grundy et al., 2002)

- Start niacin at a low dose and titrate to a higher dose over a period of weeks as tolerated.
- Take niacin with food or premedicate with aspirin 325 mg 30 minutes before niacin dosing to alleviate flushing symptoms.
- If an extended-release preparation is used, increase the dose of extended-release niacin from 500 mg to a maximum of 2,000 mg/day over 4 to 8 weeks, with the dose of extended-release niacin increasing not more than weekly.
- If immediate-release niacin is chosen, start at a dose of 100 mg 3 times daily and up-titrate to 3 g/day, divided into 2 or 3 doses.

Safety of Bile Acid Sequestrants (BAS)

1. BAS should not be used in individuals with baseline fasting triglyceride levels ≥ 300 mg/dL or type III hyperlipoproteinemia, because severe triglyceride elevations might occur. (A fasting lipid panel should be obtained before BAS is initiated, 3 months after initiation, and every 6 to 12 months thereafter.) NHLBI Grade: C (Weak); ACC/AHA COR: III: Harm; ACC/AHA LOE: B

2. It is reasonable to use BAS with caution if baseline triglyceride levels are 250 to 299 mg/dL, and evaluate a fasting lipid panel in 4 to 6 weeks after initiation. Discontinue the BAS if triglycerides exceed 400 mg/dL. NHLBI Grade: E (Expert Opinion); ACC/AHA COR: IIa; ACC/AHA LOE: C (Crouse, 1987)

Safety of Cholesterol-Absorption Inhibitors

1. It is reasonable to obtain baseline hepatic transaminases before initiation of ezetimibe. When ezetimibe is coadministered with a statin, monitor transaminase levels as clinically indicated, and discontinue ezetimibe if persistent ALT elevations ≥ 3 times ULN occur. NHLBI Grade: C (Weak);

Safety of Fibrates

1. Gemfibrozil should not be initiated in patients on statin therapy because of an increased risk for muscle symptoms and rhabdomyolysis. NHLBI Grade: B (Moderate); ACC/AHA COR: III: Harm; ACC/AHA LOE: B

2. Fenofibrate may be considered concomitantly with a low- or moderate-intensity statin only if the benefits from ASCVD risk reduction or triglyceride lowering when triglycerides are ≥ 500 mg/dL are judged to outweigh the potential risk for adverse effects. NHLBI Grade: E (Expert Opinion); ACC/AHA COR: IIb; ACC/AHA LOE: C (ACCORD Study Group et al., 2010)

3. Renal status should be evaluated before fenofibrate initiation, within 3 months after initiation, and every 6 months thereafter. Assess renal safety with both a serum creatinine level and an estimated glomerular filtration rate (eGFR) based on creatinine. NHLBI Grade: B (Moderate); ACC/AHA COR: I; ACC/AHA LOE: B

- Fenofibrate should not be used if moderate or severe renal impairment, defined as eGFR < 30 mL/min per 1.73 m^2 , is present. ACC/AHA COR: III: Harm; ACC/AHA LOE: B
- If eGFR is between 30 and 59 mL/min per 1.73 m^2 , the dose of fenofibrate should not exceed 54 mg/day.*
- If, during follow-up, the eGFR decreases persistently to ≤ 30 mL/min per 1.73 m^2 , fenofibrate should be discontinued.

*Consult the manufacturer's prescribing information as there are several forms of fenofibrate available.

Safety of Omega-3 Fatty Acids

1. If eicosapentaenoic acid (EPA) and/or docosahexanoic acid (DHA) are used for the management of severe hypertriglyceridemia, defined as triglycerides ≥ 500 mg/dL, it is reasonable to evaluate the patient for gastrointestinal disturbances, skin changes, and bleeding. NHLBI Grade: C (Weak); ACC/AHA COR: IIa; ACC/AHA LOE: B

Recommendations for Monitoring, Optimizing, and Addressing Insufficient Response to Statin Therapy

Monitoring Statin Therapy

1. Adherence to medication and lifestyle, therapeutic response to statin therapy, and safety should be regularly assessed. This should also include a fasting lipid panel performed within 4–12 weeks after initiation or dose adjustment, and every 3–12 months thereafter. Other safety measurements should be measured as clinically indicated. NHLBI Grade: A (Strong); ACC/AHA COR: I; ACC/AHA LOE: A

Optimizing Statin Therapy

1. The maximum tolerated intensity of statin should be used in individuals for whom a high- or moderate-intensity statin is recommended but not tolerated. NHLBI Grade: B (Moderate); ACC/AHA COR: I*; ACC/AHA LOE: B

Insufficient Response to Statin Therapy

1. In individuals who have a less-than-anticipated therapeutic response or are intolerant of the recommended intensity of statin therapy, the following should be performed: NHLBI Grade A (Strong); ACC/AHA COR: I; ACC/AHA LOE: A

- Reinforce medication adherence.
- Reinforce adherence to intensive lifestyle changes.
- Exclude secondary causes of hyperlipidemia.

2. It is reasonable to use the following as indicators of anticipated therapeutic response to the recommended intensity of statin therapy. Focus is on the intensity of the statin therapy. As an aid to monitoring: NHLBI Grade: E (Expert Opinion); ACC/AHA COR: IIa; ACC/AHA LOE: B (LaRosa et al., 2005; Pedersen et al., 2005; Cannon et al., 2004; Amarenco et al., 2006; Thompson & HEART-UK LDL Apheresis Working Group, 2008; Schwartz & Badellino, 2008)

- High-intensity statin therapy† generally results in an average LDL-C reduction of $\geq 50\%$ from the untreated baseline.
- Moderate-intensity statin therapy generally results in an average LDL-C reduction of 30% to $< 50\%$ from the untreated baseline.
- LDL-C levels and percents reduction are to be used only to assess response to therapy and adherence. They are not to be used as performance standards.

3. In individuals at higher ASCVD risk receiving the maximum tolerated intensity of statin therapy who continue to have a less-than-anticipated therapeutic response, addition of nonstatin cholesterol-lowering drug(s) may be considered if the ASCVD risk-reduction benefits outweigh the potential for adverse effects. Higher-risk individuals include: NHLBI Grade: E (Expert Opinion); ACC/AHA COR: IIb; ACC/AHA LOE: C (AIM-HIGH Investigators et al., 2011; ACCORD Study Group et al., 2010; Rossebo et al., 2007; Sharp Collaborative Group, 2010; Yokoyama, Origasa, & JELIS Investigators, 2003)

- Individuals with *clinical* ASCVD[‡] <75 years of age.
- Individuals with baseline LDL-C \geq 190 mg/dL.
- Individuals 40 to 75 years of age with diabetes.

Preference should be given to nonstatin cholesterol-lowering drugs shown to reduce ASCVD events in RCTs.

4. In individuals who are candidates for statin treatment but are completely statin intolerant, it is reasonable to use nonstatin cholesterol-lowering drugs that have been shown to reduce ASCVD events in RCTs if the ASCVD risk-reduction benefits outweigh the potential for adverse effects. NHLBI Grade: E (Expert Opinion); ACC/AHA COR: IIa; ACC/AHA LOE: B (Eckel, 2010; "Clofibrate and niacin in coronary heart disease," 1975; Frick et al., 1987; Lipid Research Clinics Program, 1984; "The Lipid Research Clinics Coronary Primary Prevention Trial results. II.," 1984; Rubins et al., 1999; Keech et al., 2005; HPS2-THRIVE Collaborative Group, 2013)

*Several RCTs found that low-intensity and low-moderate-intensity statin therapy reduced ASCVD events. In addition, the Cholesterol Treatment Trialists meta-analyses found that each 39-mg/dL reduction in LDL-C reduces ASCVD risk by 22%. Therefore, the Panel considered that submaximal statin therapy should be used to reduce ASCVD risk in those unable to tolerate moderate- or high-intensity statin therapy.

†In those already on a statin, in whom baseline LDL-C is unknown, an LDL-C level <100 mg/dL was observed in most individuals receiving high-intensity statin therapy.

‡Clinical ASCVD includes acute coronary syndromes, or a history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin.

Definitions:

NHLBI Grading of the Strength of Recommendations

Grade	Strength of Recommendation*
A	Strong recommendation There is high certainty based on evidence that the net benefit [†] is substantial.
B	Moderate recommendation There is moderate certainty based on evidence that the net benefit is moderate to substantial, or there is high certainty that the net benefit is moderate.
C	Weak recommendation There is at least moderate certainty based on evidence that there is a small net benefit.
D	Recommendation against There is at least moderate certainty based on evidence that there is no net benefit or that risks/harms outweigh benefits.
E	Expert opinion ("There is insufficient evidence or evidence is unclear or conflicting, but this is what the Work Group recommends.") Net benefit is unclear. Balance of benefits and harms cannot be determined because of no evidence, insufficient evidence, unclear evidence, or conflicting evidence, but the Work Group thought it was important to provide clinical guidance and make a recommendation. Further research is recommended in this area.
N	No recommendation for or against ("There is insufficient evidence or evidence is unclear or conflicting.") Net benefit is unclear. Balance of benefits and harms cannot be determined because of no evidence, insufficient evidence, unclear

Grade	evidence, or conflicting evidence, and the Work Group thought no recommendation should be made. Further research is recommended in this area.

*In most cases, the strength of the recommendation should be closely aligned with the quality of the evidence; however, under some circumstances, there may be valid reasons for making recommendations that are not closely aligned with the quality of the evidence (e.g., strong recommendation when the evidence quality is moderate, such as smoking cessation to reduce cardiovascular disease [CVD] risk or ordering an electrocardiogram [ECG] as part of the initial diagnostic work-up for a patient presenting with possible myocardial infarction [MI]). Those situations should be limited and the rationale explained clearly by the Work Group.

†Net benefit is defined as benefits minus risks/harms of the service/intervention.

NHLBI Quality Rating of the Strength of Evidence

Type of Evidence	Quality Rating*
<ul style="list-style-type: none"> Well-designed, well-executed† randomized controlled trials (RCTs) that adequately represent populations to which the results are applied and directly assess effects on health outcomes. Meta-analyses of such studies. <p>Highly certain about the estimate of effect. Further research is unlikely to change confidence in the estimate of effect.</p>	High
<ul style="list-style-type: none"> RCTs with minor limitations‡ affecting confidence in, or applicability of, the results. Well-designed, well-executed nonrandomized controlled studies§ and well-designed, well-executed observational studies¶. Meta-analyses of such studies. <p>Moderately certain about the estimate of effect. Further research may have an impact on confidence in the estimate of effect and may change the estimate.</p>	Moderate
<ul style="list-style-type: none"> RCTs with major limitations. Nonrandomized controlled studies and observational studies with major limitations affecting confidence in, or applicability of, the results. Uncontrolled clinical observations without an appropriate comparison group (e.g., case series, case reports). Physiological studies in humans. Meta-analyses of such studies. <p>Low certainty about the estimate of effect. Further research is likely to have an impact on confidence in the estimate of effect and is likely to change the estimate.</p>	Low

*In some cases, other evidence, such as large all-or-none case series (e.g., jumping from airplanes or tall structures), can represent high- or moderate-quality evidence. In such cases, the rationale for the evidence rating exception should be explained by the Work Group and clearly justified.

†"Well-designed, well-executed" refers to studies that directly address the question; use adequate randomization, blinding, and allocation concealment; are adequately powered; use intention-to-treat analyses; and have high follow-up rates.

‡Limitations include concerns with the design and execution of a study that result in decreased confidence in the true estimate of the effect. Examples of such limitations include but are not limited to: inadequate randomization, lack of blinding of study participants or outcome assessors, inadequate power, outcomes of interest that are not prespecified for the primary outcomes, low follow-up rates, and findings based on subgroup analyses. Whether the limitations are considered minor or major is based on the number and severity of flaws in design or execution. Rules for determining whether the limitations are considered minor or major and how they will affect rating of the individual studies will be developed collaboratively with the methodology team.

§Nonrandomized controlled studies refer to intervention studies where assignment to intervention and comparison groups is not random (e.g., quasi-experimental study design).

¶Observational studies include prospective and retrospective cohort, case-control, and cross-sectional studies.

Applying Classification of Recommendations and Level of Evidence

		Size of Treatment Effect								
		CLASS I <i>Benefit >>> Risk</i> Procedure/Treatment SHOULD be performed/ administered	CLASS IIa <i>Benefit >> Risk</i> <i>Additional studies with focused objectives needed</i> IT IS REASONABLE to perform procedure/administer treatment	CLASS IIb <i>Benefit ≥ Risk</i> <i>Additional studies with broad objectives needed; additional registry data would be helpful</i> Procedure/Treatment MAY BE CONSIDERED	CLASS III <i>No Benefit</i> or Class III <i>Harm</i>					
						Procedure/Test	Treatment			
					COR III: No Benefit	Not helpful	No proven benefit			
					COR III: Harm	Excess cost without benefit or harmful	Harmful to patients			
Estimate of Certainty (Precision) of Treatment Effect	LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	<ul style="list-style-type: none">Recommendation that procedure or treatment is useful/effectiveSufficient evidence from multiple randomized trials or meta-analyses	<ul style="list-style-type: none">Recommendation in favor of treatment or procedure being useful/effectiveSome conflicting evidence from multiple randomized trials or meta-analyses	<ul style="list-style-type: none">Recommendation's usefulness/efficacy less well establishedGreater conflicting evidence from multiple randomized trials or meta-analyses	<ul style="list-style-type: none">Recommendation that procedure or treatment is not useful/effective and may be harmfulSufficient evidence from multiple randomized trials or meta-analyses					
	LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	<ul style="list-style-type: none">Recommendation that procedure or treatment is useful/effectiveEvidence from single randomized trial or nonrandomized studies	<ul style="list-style-type: none">Recommendation in favor of treatment or procedure being useful/effectiveSome conflicting evidence from single randomized trial or nonrandomized studies	<ul style="list-style-type: none">Recommendation's usefulness/efficacy less well establishedGreater conflicting evidence from single randomized trial or nonrandomized studies	<ul style="list-style-type: none">Recommendation that procedure or treatment is not useful/effective and may be harmfulEvidence from single randomized trial or nonrandomized studies					
	LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	<ul style="list-style-type: none">Recommendation that procedure or treatment is useful/effectiveOnly expert opinion, case studies, or standard of care	<ul style="list-style-type: none">Recommendation in favor of treatment or procedure being useful/effectiveOnly diverging expert opinion, case studies, or standard of care	<ul style="list-style-type: none">Recommendation's usefulness/efficacy less well establishedOnly diverging expert opinion, case studies, or standard of care	<ul style="list-style-type: none">Recommendation that procedure or treatment is not useful/effective and may be harmfulOnly expert opinion, case studies, or standard of care					

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

†For comparative-effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

Clinical Algorithm(s)

The following algorithms are provided in the original guideline document:

- Summary of Statin Initiation Recommendations for the Treatment of Blood Cholesterol to Reduce ASCVD Risk in Adults
- Initiating Statin Therapy in Individuals with Clinical ASCVD
- Initiating Statin Therapy in Individuals without Clinical ASCVD
- Statin Therapy: Monitoring Therapeutic Response and Adherence

Scope

Disease/Condition(s)

- High blood cholesterol (hyperlipidemia)
- Atherosclerotic cardiovascular disease (ASCVD) including coronary heart disease (CHD), stroke, and peripheral arterial disease of

presumed atherosclerotic origin

Guideline Category

Prevention

Risk Assessment

Treatment

Clinical Specialty

Cardiology

Endocrinology

Family Practice

Geriatrics

Internal Medicine

Nutrition

Pharmacology

Preventive Medicine

Intended Users

Advanced Practice Nurses

Dietitians

Health Care Providers

Nurses

Pharmacists

Physician Assistants

Physicians

Guideline Objective(s)

- To update the clinical practice recommendations for the treatment of blood cholesterol levels to reduce atherosclerotic cardiovascular disease (ASCVD) risk using data from randomized controlled trials (RCTs) and systematic reviews and meta-analyses of RCTs
- To provide a strong, evidence-based foundation for the treatment of cholesterol for the primary and secondary prevention of ASCVD in women and men

Target Population

Adults ≥ 21 years of age at risk of or with atherosclerotic cardiovascular disease (ASCVD)

Interventions and Practices Considered

1. Establishing specific low-density lipoprotein cholesterol (LDL-C) or non-high-density lipoprotein cholesterol (non-HDL-C) targets for the primary or secondary prevention of atherosclerotic cardiovascular disease (ASCVD) (no recommendation made)
2. Statin therapy for secondary prevention of ASCVD (high-intensity or moderate-intensity therapy)
3. Primary prevention in individuals ≥ 21 years of age with LDL-C ≥ 190 mg/dL
 - Identifying secondary causes of hyperlipidemia
 - High-intensity statin therapy
 - Maximum tolerated statin intensity
 - Addition of non-statin drug therapy
 - Evaluation of adverse effects, drug interactions, and ASCVD risk-reduction benefits
4. Primary prevention in individuals with diabetes and LDL-C 70–189 mg/dL
 - Moderate- or high-intensity statin therapy
 - Evaluation of adverse effects, drug interactions, and ASCVD risk-reduction benefits
5. Primary prevention in individuals without diabetes and with LDL-C 70–189 mg/dL
 - Use of the Pooled Cohort Equations to estimate 10-year ASCVD risk for individuals without clinical ASCVD to guide initiation of statin therapy
 - Discussing potential for ASCVD risk-reduction benefits and for adverse effects and drug–drug interactions, as well as patient preferences for treatment
6. Initiation or discontinuation of statins in patients with New York Heart Association (NYHA) class II–IV ischemic systolic heart failure or in patients on maintenance hemodialysis (no recommendation made)
7. Safety considerations for use of statin therapy
8. Safety consideration for use of non-statin therapy (niacin, bile acid sequestrants, cholesterol-absorption inhibitors, fibrates, omega-3 fatty acids)
9. Monitoring, optimizing, and addressing insufficient response to statin therapy

Major Outcomes Considered

- Low-density lipoprotein cholesterol (LDL-C) levels or non-high-density lipoprotein cholesterol (non-HDL-C) levels at baseline and follow-up
- Acute coronary syndromes (unstable angina, ST segment elevation myocardial infarction [STEMI], non-ST segment elevation myocardial infarction [NSTEMI])
- Stroke: fatal and nonfatal and stroke by type (ischemic, hemorrhagic, embolic, other)
- Coronary revascularization procedures: angioplasty, coronary stent placement, coronary artery bypass graft (CABG)
- Noncoronary revascularization procedures: carotid, lower extremity, abdominal aortic aneurysm (AAA) repair
- New-onset heart failure
- Sudden cardiac death
- Silent myocardial infarction
- Hospitalization for heart failure
- Hospitalization for any coronary heart disease (CHD) or cardiovascular disease (CVD) cause
- Cognitive function or dementia
- Stage 3 chronic kidney disease (CKD) or dialysis or impaired estimated glomerular filtration rate (eGFR) (<15 , <30 , or <60 mL/min/1.73m²) or albuminuria CHD, CVD, non-CVD, and total mortality
- Calculated 10-year Framingham risk score for CHD or CVD
- Rhabdomyolysis or myositis or myopathy (creatinine kinase [CK] higher than 10 times the upper limit of normal [ULN], CK 3 to 10 times ULN)
- Cancer incidence (site specific and total) and cancer mortality

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Literature Search Infrastructure, Search Strategy Development, and Validation

The literature search was performed using an integrated suite of search engines that explored a central repository of citations and full-text journal articles. The central repository, search engines, search results, and web-based modules for literature screening and data abstraction were integrated within a technology platform called the Virtual Collaborative Workspace (VCW). The VCW was custom-developed for the National Heart, Lung and Blood Institute (NHLBI) guidelines initiative.

The central repository consisted of 1.9 million citations and 71,000 full text articles related to cardiovascular disease (CVD) risk reduction. Citations were acquired from PubMed, EMBASE, CINAHL, Cochrane, PsycINFO, Wilson Science, and Biological Abstracts databases. Literature searches were conducted using a collection of search engines including: TeraText®, Content Analyst, and Collexis, and Lucene. These engines were used for executing search strategies; Lucene was used in correlating the search with screening results.

For every critical question (CQ), literature search and screening were conducted according to the understanding of the question and the inclusion and exclusion (I/E) criteria that provided specific characteristics of studies relevant to the question. Criteria were framed in the PICOTSS format. The question and PICOTSS components were translated into a search strategy involving Boolean and conceptual queries.

A Boolean query encodes both inclusion and exclusion rules. It grants access to the maximum quantity of citations, which are then analyzed by text-analytics tools and ranked to produce a selection for literature screening that was conducted by two independent reviewers in the VCW's web-based module. Boolean queries select citations by matching words in titles and abstracts, as well as Medical Subject Headings (MeSH) and subheadings. The number of citations resulting from Boolean queries has ranged from a few hundred to several thousand, depending on the question. The text analytics tools suite included:

- A natural language processing module for automated extraction of data elements to support the application of I/E criteria. Data elements that were frequently extracted and used were study size and intervention follow-up period.
- Content Analyst for automatically expanding vocabulary of queries, conceptual retrieval, and conceptual clustering. The conceptual query engine employed in Content Analyst leverages word-frequency features and co-occurrence in similar contexts to index, select and rank results. The indexing uses the Singular Value Decomposition (SVD) algebraic method.
- TeraText for ranking search results and a variety of fast operations on the inverted index.

Search strategy development was intertwined with the results of literature screening, which provided feedback on search quality and context. Screened literature was categorized into two subsets: relevant or not relevant to the question. Next, results were analyzed to determine the characteristics of relevant versus not relevant citations. Additional keywords and MeSH terms were used to expand or contract the scope of the query as driven by characteristics of relevant citations. If a revised search strategy produced more citations than the original strategy, the new batch of citations was added for review. The search strategy refinement/literature review cycle was repeated until all citations covered by the most recent Boolean query had been screened.

Each search strategy was developed and implemented in the VCW. The search strategy was reviewed by the methodologist and panel members and was available for viewing and printing at any time by panel members and staff collaborating on the systematic review. It was available for execution and for supplying literature updates until the literature search and screening cut-off date.

Search strategies for a sample of questions were validated by an independent methodology team. This validation process involved developing and executing a separate search strategy and screening a random sample of citations against I/E criteria. These results were compared to the search and screening results developed by the systematic review team. As an additional validation method, studies identified in systematic reviews and meta-analyses were cross-checked against a critical question's "include list" to ensure completeness of the search strategy.

Process for Literature Review

Using results of the search strategy, criteria were applied to screen literature for inclusion or exclusion in the evidence base for the CQ. I/E criteria address the parameters in the PICOTSS framework and determine what types of studies are eligible and appropriate to answer the CQ. Additional criteria, such as sample-size restrictions, were included by the panel to fit the context of the CQ.

Pilot Literature Screening Mode

In the Pilot Literature Screening Mode, two reviewers independently screened the first 50 titles/abstracts in the search strategy results by applying I/E criteria. Reviewers voted to include the publication for full-text review or voted to exclude it. Reviewers compared their results to ensure that I/E criteria were applied consistently. Discrepancies in votes were discussed, and clarification on criteria was sought from the panel where appropriate. For example, if criteria were not specific enough to be clearly applied to include or exclude a citation, guidance was sought to word

criteria more explicitly.

During this phase, reviewers provided feedback to the Literature Search team about the relevance of search strategy results; the team used this feedback to further refine and optimize the search.

Phase 1: Title and Abstract Screening Phase

After the completion of the Pilot Mode phase, two reviewers independently screened search results at the title and abstract level by applying I/E criteria. Reviewers voted to include or exclude the publication for full text review.

Titles and abstracts that one or both reviewers voted to include advanced to Phase 2, Full-Text Screening. Titles and abstracts where both reviewers voted to exclude were excluded and not reviewed further. These citations are maintained in the VCW and marked as "excluded at title/abstract phase."

Phase 2: Full Text Screening Phase

Titles and abstracts that at least one reviewer voted to include were reviewed at the full-text level in Phase 2. In this Phase, two reviewers independently applied I/E criteria to the full-text article and voted for: include, exclude, or undecided. The reviewer had to specify the rationale for exclusion (e.g., population, intervention, etc.) in this phase.

Articles that both reviewers voted to include were moved to the Include List. Articles that both reviewers voted to exclude were moved to the Exclude List. These citations were maintained in the VCW and identified as "excluded at the full-article phase," and the rationale for exclusion was noted. Any article with discrepant votes (i.e., one include and one undecided, one include and one exclude) advanced to Phase 3.

Phase 3: Resolution and Consultation Phase

In this phase, reviewers discussed their discrepant votes for include, exclude, or undecided and cited the relevant criteria for their decision. The two reviewers attempted to achieve consensus through collaborative discussion. If a decision was not reached between the two reviewers, they asked the methodologist for advice. If a decision was not reached after consultation with the methodologist, the panel was consulted. However, the methodologist had the final decision. The final disposition of the article (include or exclude) was recorded in the VCW along with comments from the adjudication process.

As in the search strategies being posted and available for viewing on the VCW, all citations screened for a CQ are maintained in the VCW along with their reviewer voting status and all collected comments.

CQ1 and CQ2 Search Strategy Results

The following databases were searched for randomized controlled trials (RCTs) and systematic reviews (SRs) and meta-analyses (MAs) of RCTs to answer CQ1 and CQ2:

- PubMed from January 1998 to December 2009
- CINAHL from January 1998 to July 2008
- EMBASE from January 1998 to July 2008
- PsycINFO from January 1998 to July 2008
- Evidence-based Medicine Cochrane Libraries from January 1998 to July 2008
- Biological Abstracts from January 2004 to July 2008
- Wilson Social Sciences Abstracts from January 1998 to July 2008

Because the Panel conducted its own SR, using original publications dating back to 1998, SRs and MAs of RCTs conducted and published by others were identified, but they were not abstracted or included in the formal evidence review. However, SRs and MAs that were identified in the search and met the inclusion criteria were eligible for use as reference material in the report. The evidence and summary tables consisted only of data from the original publications of eligible RCTs, and these tables formed the basis for the panel's deliberations. Duplicate citations arising from the same citation's appearing in more than one database were removed from the Central Repository prior to screening.

CQ3 Search Strategy Results

CQ3 was initially intended to be a de novo SR of original RCTs plus SRs and MAs. In May 2011, however, scope of CQ3 was changed, and the review for statins was restricted to SRs and MAs only. SRs and MAs for the statin component of the question had to include only studies that met the CQ3 I/E criteria and report statin-only outcomes. MAs that covered both statin and nonstatin therapies were included if they stratified estimates by drug class.

The review for the following drug therapies used to treat dyslipidemia remained a de novo SR of RCTs: gemfibrozil; fenofibrate; nicotinic acid or niacin; bile acid sequestrants (BAS), including bile acid resins; ezetimibe; and omega-3 fatty acids.

The search included the following bibliographic databases:

- PubMed from January 1975 to May 2011
 - Search for de novo SR: January 1975 to January 2010
 - Supplemental search for statin-related SRs and MAs and nonstatin-related studies: January 2010 to May 2011
- CINAHL from January 1998 to July 2008
- EMBASE from January 1998 to July 2008
- PsycINFO from January 1998 to July 2008
- EBM (Evidence-based Medicine) Cochrane Libraries from January 1998 to July 2008
- Biological Abstracts from January 2004 to July 2008
- Wilson Social Sciences Abstracts from January 1998 to July 2008

Duplicate citations arising from the same citation's being found in more than one database were removed from the Central Repository before screening.

Number of Source Documents

Critical Question (CQ) 1 Search Strategy Results

The search produced 2,196 citations. Twenty-eight additional citations, 24 of which were published after December 2009, were added for review. Six of these 24 citations were included because they met the eligibility criteria; four were randomized controlled trials (RCTs; ACCORD, AIM-HIGH, SEARCH, and SHARP). Three citations published before 1998 were also reviewed but were excluded because they did not meet the criteria for review. One citation for SPARCL was missed by the initial search because it was not annotated for the RCT MeSH term. However, this publication met the inclusion criteria and was subsequently included. The titles and abstracts of these 2,224 publications were screened against the inclusion/exclusion (I/E) criteria independently by two reviewers, resulting in the retrieval of 367 full-text papers. The full-text papers were independently screened by two reviewers, and 299 of these publications were excluded based on one or more of the I/E criteria. An additional 21 publications were excluded, because they were rated as poor quality, using the National Heart, Lung and Blood Institute (NHLBI) Quality-Assessment Tool for Controlled Intervention Studies. Forty-seven RCTs were included in the CQ1 evidence base.

CQ2 Search Strategy Results

The search, which had a cutoff date of December 2009, produced 1,921 citations. Thirty-five additional citations published after December 2009 were added for review. Some of these citations were retrieved because of overlap with the 2010 citations resulting from the final refresh of the Central Repository executed on January 30, 2010. A few additional citations were eligible for review according to criteria set forth by the NHLBI and the Adult Treatment Panel (ATP). Four of the 35 citations published after December 2009 met the eligibility criteria; all 4 were publications related to the JUPITER trial. Two were subsequently excluded because they were rated as poor quality. The titles and abstracts of these 1,956 publications were screened against the I/E criteria independently by two reviewers, resulting in the retrieval of 270 full-text papers. These papers were independently screened by two reviewers, and 244 of these publications were excluded based on one or more of the I/E criteria. An additional four publications were excluded, because they were rated as poor quality using the NHLBI Quality-Assessment Tool for Controlled Intervention Studies. Twenty-two RCTs were included in the CQ2 Evidence Base.

CQ3 Search Strategy Results

The search produced 7,551 citations. Three additional citations published after May 2011 were added, because they were eligible for review according to criteria set forth by NHLBI and the ATP. Two of the three citations were RCTs and one was a meta-analysis (MA). A natural-language processing filter was used to identify studies with sample sizes less than 1,000 for each arm or less than 3,000 for the entire study and studies with follow-up of less than 12 months. The natural-language processing filter was executed against titles and abstracts and automatically excluded 4,640 publications. The titles and abstracts of the remaining 2,914 publications were screened against the I/E criteria independently by two reviewers, resulting in the retrieval of 813 full-text papers. These papers were independently screened by two reviewers, and 751 of these papers were excluded based on one or more of the I/E criteria. An additional 24 publications—3 systematic reviews or MAs and 21 RCTs—were excluded because they were rated as poor quality. Thirty-eight publications were included in the CQ3 Evidence Base.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Applying Classification of Recommendations and Level of Evidence

		Size of Treatment Effect												
		CLASS I	CLASS IIa	CLASS IIb	CLASS III <i>No Benefit</i> or Class III <i>Harm</i>									
		<i>Benefit >>> Risk</i> Procedure/Treatment SHOULD be performed/ administered	<i>Benefit >> Risk</i> <i>Additional studies with focused objectives needed</i> IT IS REASONABLE to perform procedure/administer treatment	<i>Benefit ≥ Risk</i> <i>Additional studies with broad objectives needed; additional registry data would be helpful</i> Procedure/Treatment MAY BE CONSIDERED	<table><tr><td></td><td>Procedure/Test</td><td>Treatment</td></tr><tr><td>COR III: No Benefit</td><td>Not helpful</td><td>No proven benefit</td></tr><tr><td>COR III: Harm</td><td>Excess cost without benefit or harmful</td><td>Harmful to patients</td></tr></table>		Procedure/Test	Treatment	COR III: No Benefit	Not helpful	No proven benefit	COR III: Harm	Excess cost without benefit or harmful	Harmful to patients
	Procedure/Test	Treatment												
COR III: No Benefit	Not helpful	No proven benefit												
COR III: Harm	Excess cost without benefit or harmful	Harmful to patients												
Estimate of Certainty (Precision) of Treatment Effect	LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	<ul style="list-style-type: none">Recommendation that procedure or treatment is useful/effectiveSufficient evidence from multiple randomized trials or meta-analyses	<ul style="list-style-type: none">Recommendation in favor of treatment or procedure being useful/effectiveSome conflicting evidence from multiple randomized trials or meta-analyses	<ul style="list-style-type: none">Recommendation's usefulness/efficacy less well establishedGreater conflicting evidence from multiple randomized trials or meta-analyses	<ul style="list-style-type: none">Recommendation that procedure or treatment is not useful/effective and may be harmfulSufficient evidence from multiple randomized trials or meta-analyses									
	LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	<ul style="list-style-type: none">Recommendation that procedure or treatment is useful/effectiveEvidence from single randomized trial or nonrandomized studies	<ul style="list-style-type: none">Recommendation in favor of treatment or procedure being useful/effectiveSome conflicting evidence from single randomized trial or nonrandomized studies	<ul style="list-style-type: none">Recommendation's usefulness/efficacy less well establishedGreater conflicting evidence from single randomized trial or nonrandomized studies	<ul style="list-style-type: none">Recommendation that procedure or treatment is not useful/effective and may be harmfulEvidence from single randomized trial or nonrandomized studies									
	LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	<ul style="list-style-type: none">Recommendation that procedure or treatment is useful/effectiveOnly expert opinion, case studies, or standard of care	<ul style="list-style-type: none">Recommendation in favor of treatment or procedure being useful/effectiveOnly diverging expert opinion, case studies, or standard of care	<ul style="list-style-type: none">Recommendation's usefulness/efficacy less well establishedOnly diverging expert opinion, case studies, or standard of care	<ul style="list-style-type: none">Recommendation that procedure or treatment is not useful/effective and may be harmfulOnly expert opinion, case studies, or standard of care									

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

†For comparative-effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

National Heart, Lung and Blood Institute (NHLBI) Quality Rating of the Strength of Evidence

Type of Evidence	Quality Rating*
<ul style="list-style-type: none"> Well-designed, well-executed† randomized controlled trials (RCTs) that adequately represent populations to which the results are applied and directly assess effects on health outcomes. Meta-analyses of such studies. <p>Highly certain about the estimate of effect. Further research is unlikely to change confidence in the estimate of effect.</p>	High
<ul style="list-style-type: none"> RCTs with minor limitations‡ affecting confidence in, or applicability of, the results. 	Moderate

Type of Evidence <ul style="list-style-type: none"> • Well-designed, well-executed nonrandomized controlled studies§ and well-designed, well-executed observational studies¶. • Meta-analyses of such studies. 	Quality Rating*
Moderately certain about the estimate of effect. Further research may have an impact on confidence in the estimate of effect and may change the estimate.	
<ul style="list-style-type: none"> • RCTs with major limitations. • Nonrandomized controlled studies and observational studies with major limitations affecting confidence in, or applicability of, the results. • Uncontrolled clinical observations without an appropriate comparison group (e.g., case series, case reports). • Physiological studies in humans. • Meta-analyses of such studies. <p>Low certainty about the estimate of effect. Further research is likely to have an impact on confidence in the estimate of effect and is likely to change the estimate.</p>	Low

*In some cases, other evidence, such as large all-or-none case series (e.g., jumping from airplanes or tall structures), can represent high- or moderate-quality evidence. In such cases, the rationale for the evidence rating exception should be explained by the Work Group and clearly justified.

†"Well-designed, well-executed" refers to studies that directly address the question; use adequate randomization, blinding, and allocation concealment; are adequately powered; use intention-to-treat analyses; and have high follow-up rates.

‡Limitations include concerns with the design and execution of a study that result in decreased confidence in the true estimate of the effect. Examples of such limitations include but are not limited to: inadequate randomization, lack of blinding of study participants or outcome assessors, inadequate power, outcomes of interest that are not prespecified for the primary outcomes, low follow-up rates, and findings based on subgroup analyses. Whether the limitations are considered minor or major is based on the number and severity of flaws in design or execution. Rules for determining whether the limitations are considered minor or major and how they will affect rating of the individual studies will be developed collaboratively with the methodology team.

§Nonrandomized controlled studies refer to intervention studies where assignment to intervention and comparison groups is not random (e.g., quasi-experimental study design).

¶Observational studies include prospective and retrospective cohort, case-control, and cross-sectional studies.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Directed by the National Heart, Lung and Blood Institute (NHLBI), with support from the Expert Panels and Work Groups, the contractor staff:

- Determined, by two independent raters, the quality of each included study. The methodology staff, with input from NHLBI, adapted study-rating instruments and trained study raters on the use of these instruments.
- Abstracted relevant information from the included studies into an electronic database. Templates with lists of data elements pertinent to the established inclusion/exclusion (I/E) criteria were constructed and used to support abstraction.
- Constructed detailed evidence tables, which organized the data from the abstraction database.
- Analyzed the evidence tables and constructed summary tables, which display the evidence in a manageable format to answer specific parts of the critical question (CQ) (see Appendix H in the full panel report supplement [see the "Availability of Companion Documents" field]).

The Expert Panels and Work Groups:

- Used summary tables to develop evidence statements for each CQ. The quality of evidence for each evidence statement was graded as

high, moderate, or low on the basis of scientific methodology, scientific strength, and consistency of results (see the "Rating Scheme for the Strength of the Evidence" field).

See Appendix A in the full panel report supplement (see the "Availability of Companion Documents" field) for further details of each step in the systematic evidence review process. The strength of the body of evidence represents the degree of certainty, based on the overall body of evidence, that an effect or association is correct. Appendix A describes how four domains of the body of evidence—consistency, directness, precision, and risk for bias—were used to grade the strength of evidence.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The American College of Cardiology (ACC) and American Heart Association (AHA) have collaborated with the National Heart, Lung and Blood Institute (NHLBI) and stakeholder and professional organizations to develop clinical practice guidelines for assessment of cardiovascular risk, lifestyle modifications to reduce cardiovascular risk, management of blood cholesterol in adults, and management of overweight and obesity in adults.

In 2008, the NHLBI initiated these guidelines by sponsoring rigorous systematic evidence reviews for each topic by expert panels convened to develop critical questions (CQs), interpret the evidence, and craft recommendations. In response to the 2011 report from the Institute of Medicine on the development of trustworthy clinical guidelines, the NHLBI Advisory Council recommended that the NHLBI focus specifically on reviewing the highest-quality evidence and partner with other organizations to develop recommendations. Accordingly, in June 2013 the NHLBI initiated collaboration with the ACC and AHA to work with other organizations to complete and publish the four guidelines and make them available to the widest possible constituency. Recognizing that the Expert Panels/Work Groups did not consider evidence beyond 2011 (except as specified in the methodology), the ACC, AHA, and collaborating societies plan to begin updating these guidelines starting in 2014.

The joint ACC/AHA Task Force on Practice Guidelines (Task Force) appointed a subcommittee to shepherd this transition, communicate the rationale and expectations to the writing panels and partnering organizations, and expeditiously publish the documents. The ACC/AHA and partner organizations recruited a limited number of expert reviewers for fiduciary examination of content, recognizing that each document had undergone extensive peer review by representatives of the NHLBI Advisory Council, key federal agencies, and scientific experts. Each writing panel responded to comments from these reviewers. Clarifications were incorporated where appropriate, but there were no substantive changes because the bulk of the content was undisputed.

Although the Task Force led the final development of these prevention guidelines, they differ from other ACC/AHA guidelines. First, as opposed to an extensive compendium of clinical information, these documents are significantly more limited in scope and focus on selected CQs on each topic based on the highest-quality evidence available. Recommendations were derived from randomized trials, meta-analyses, and observational studies evaluated for quality and were not formulated when sufficient evidence was not available. Second, the text accompanying each recommendation is succinct, summarizing the evidence for each question. The Full Panel/Work Group Reports (see the "Availability of Companion Documents" field) include more detailed information about the evidence statements (ESs) that serve as the basis for recommendations. Third, the format of the recommendations differs from other ACC/AHA guidelines. Each recommendation has been mapped from the NHLBI grading format to the ACC/AHA Classification of Recommendation/Level of Evidence (COR/LOE) construct (see the "Rating Scheme for the Strength of the Evidence" field) and is expressed in both formats. Because of the inherent differences in grading systems and the clinical questions driving the recommendations, alignment between the NHLBI and ACC/AHA formats is in some cases imperfect. Explanations of these variations are noted in the recommendation tables, where applicable.

Organization of the Panel

The Blood Cholesterol Expert Panel (Expert Panel) was originally convened as the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel IV) appointed by the NHLBI. The Expert Panel was composed of 13 members and 3 ex-officio members, which included primary care physicians, cardiologists, endocrinologists, and experts in clinical lipidology, clinical trials, cardiovascular epidemiology and nutrition, and guideline development.

The Expert Panel chair asked all panel members to disclose any conflict-of-interest information to the full panel in advance of the deliberations; members with conflicts were asked to recuse themselves from voting on any aspect of the guideline for which a conflict might exist. All 16 members of the NHLBI Adult Treatment Panel IV Panel transitioned to the ACC/AHA guideline Expert Panel. Independent contractors

performed the systematic review with the assistance of the Expert Panel and provided methodological guidance to the Expert Panel.

CQ-Based Approach

The body of this report is organized by CQ. For each CQ:

- The rationale for its selection is provided and methods described.
- The body of evidence is summarized, and evidence statements, which include a rating for quality, are presented. A narrative summary also supports each evidence statement.
- Recommendations and recommendation strength are accompanied by a summary of how the recommendation derives from the evidence and a discussion of issues considered by the Expert Panel in formulating the recommendation.

Description of How Panels Developed and Prioritized Critical Questions

After panels were convened, members were invited to submit topic areas or questions for systematic review. Members were asked to identify topics of the greatest relevance and impact for the target audience of the guideline: primary care providers (PCPs).

Proposed questions and topic areas were collected from panel members over a period of several months. The number of CQs was scoped and then prioritized based on resource constraints. After group discussion, panel members ranked priority CQs through collaborative dialogue and voting. The rationale for each priority CQ is addressed in the main report (see the "Availability of Companion Documents" field).

With support from the methodologist and systematic review team, priority CQs were formulated. Inclusion and exclusion (I/E) criteria were defined and formatted using the PICOTSS framework. PICOTSS is a framework for a structured research question and includes the following components in the statement of the critical question or in the question's I/E criteria: person/population, intervention/exposure, comparator, outcome, timing, setting, study design.

I/E criteria define the parameters for the selection of literature for a particular critical question. They were developed with input from the methodologist and systematic review team to ensure that criteria were clear and precise and could be applied consistently across literature identified in the search.

The final CQs and criteria were submitted to the Literature Search team for search strategy development.

The three CQs are as follows:

CQ1. What is the evidence for low-density lipoprotein cholesterol (LDL-C) and non-high-density lipoprotein cholesterol (non-HDL-C) goals for the secondary prevention of atherosclerotic cardiovascular disease (ASCVD)?

CQ2. What is the evidence for LDL-C and non-HDL-C goals for the primary prevention of ASCVD?

CQ3. For primary and secondary prevention, what is the impact on lipid levels, effectiveness, and safety of specific cholesterol-modifying drugs used for lipid management in general and in selected subgroups?

Process for Developing Evidence Statements, Recommendations, and Panel Voting

Using the Summary Tables (and Evidence Tables as needed), Evidence Statements were collaboratively written by expert panel members with input from methodology staff and oversight of the process by NHLBI staff. Evidence Statements aimed to summarize key messages from the evidence that could be provided to primary care physicians and other stakeholders. In some cases, the evidence was too limited or inconclusive, so no Evidence Statement was developed, or a statement of insufficient evidence was made.

Methodology staff provided expert panels with overarching guidance on how to grade the level of evidence (high, moderate, low), and the panels used this guidance to grade each Evidence Statement.

Voting occurred by a Panel Chair asking each member to signify his or her vote or via anonymous e-mail ballots. NHLBI project staff, methodologists, and contractors did not vote.

Once Evidence Statements were finalized, attention turned to Recommendations. Recommendations were developed using a similar process to that for the Evidence Statements. For approval of a Recommendation rated E (expert opinion), at least 75% of the expert panel members had to vote "yes." For both Evidence Statements and Recommendations, voting could be open so that differing viewpoints could be identified easily and further discussion and revisions facilitated to address areas of disagreement (e.g., by crafting language or dividing an evidence statement into more than one statement). Voting also could be by confidential ballot if the group so chose.

For both Evidence Statements and Recommendations, a record of the vote count (for, against, abstain, recuse) was made without attribution. The ideal was 100% consensus, but a two-thirds majority was considered acceptable.

Rating Scheme for the Strength of the Recommendations

Note: Each recommendation has been mapped from the National Heart, Lung and Blood Institute (NHLBI) grading format below to the American College of Cardiology/American Heart Association (ACC/AHA) Classification of Recommendation/Level of Evidence (COR/LOE) construct (see the "Rating Scheme for the Strength of the Evidence" field) and is expressed in both formats.

NHLBI Grading of the Strength of Recommendations

Grade	Strength of Recommendation*
A	Strong recommendation There is high certainty based on evidence that the net benefit† is substantial.
B	Moderate recommendation There is moderate certainty based on evidence that the net benefit is moderate to substantial, or there is high certainty that the net benefit is moderate.
C	Weak recommendation There is at least moderate certainty based on evidence that there is a small net benefit.
D	Recommendation against There is at least moderate certainty based on evidence that there is no net benefit or that risks/harms outweigh benefits.
E	Expert opinion ("There is insufficient evidence or evidence is unclear or conflicting, but this is what the Work Group recommends.") Net benefit is unclear. Balance of benefits and harms cannot be determined because of no evidence, insufficient evidence, unclear evidence, or conflicting evidence, but the Work Group thought it was important to provide clinical guidance and make a recommendation. Further research is recommended in this area.
N	No recommendation for or against ("There is insufficient evidence or evidence is unclear or conflicting.") Net benefit is unclear. Balance of benefits and harms cannot be determined because of no evidence, insufficient evidence, unclear evidence, or conflicting evidence, and the Work Group thought no recommendation should be made. Further research is recommended in this area.

*In most cases, the strength of the recommendation should be closely aligned with the quality of the evidence; however, under some circumstances, there may be valid reasons for making recommendations that are not closely aligned with the quality of the evidence (e.g., strong recommendation when the evidence quality is moderate, such as smoking cessation to reduce cardiovascular disease [CVD] risk or ordering an electrocardiogram [ECG] as part of the initial diagnostic work-up for a patient presenting with possible myocardial infarction [MI]). Those situations should be limited and the rationale explained clearly by the Work Group.

†Net benefit is defined as benefits minus risks/harms of the service/intervention.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Description of Method of Guideline Validation

A formal peer review process was initially completed under the auspices of the National Heart, Lung and Blood Institute (NHLBI) and included 23 expert reviewers and representatives of federal agencies. This document was also reviewed by 4 expert reviewers nominated by the American College of Cardiology (ACC) and the American Heart Association (AHA) when the management of the guideline transitioned to the ACC/AHA.

This document was approved for publication by the governing bodies of the ACC and AHA and endorsed by the American Academy of Physician Assistants, American Association of Cardiovascular and Pulmonary Rehabilitation, American Pharmacists Association, American Society for Preventive Cardiology, Association of Black Cardiologists, Preventive Cardiovascular Nurses Association, and WomenHeart: The National Coalition for Women with Heart Disease.

This document was approved by the American College of Cardiology Board of Trustees and the American Heart Association Science Advisory and Coordinating Committee in November 2013. The Academy of Nutrition and Dietetics affirms the value of this guideline.

Evidence Supporting the Recommendations

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Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease (ASCVD) risk and prevent both nonfatal and fatal ASCVD events

Potential Harms

- Adverse effects of statin and nonstatin medications. A conservative estimate of adverse events of statin use includes excess cases of new-onset diabetes and rare cases of myopathy and hemorrhagic stroke. The rate of excess diabetes varies by statin intensity.
- Drug-drug interactions
- See "Statin Safety Recommendations" and "Nonstatin Safety Recommendations" in the "Major Recommendations" field.

Contraindications

Contraindications

- Unexplained alanine transaminase (ALT) ≥ 3 times upper limit of normal (ULN) is a contraindication to statin therapy as listed in manufacturer's prescribing information.
- Treatment with statins, niacin, and ezetimibe are contraindicated during pregnancy and lactation. Statins are listed as pregnancy category X and should not be used in women of childbearing potential unless these women are using effective contraception and are not nursing.

Qualifying Statements

Qualifying Statements

These guidelines are meant to define practices that meet the needs of patients in most circumstances and are not a replacement for clinical judgment. The ultimate decision about care of a particular patient must be made by the healthcare provider and patient in light of the circumstances presented by that patient. As a result, situations might arise in which deviations from these guidelines may be appropriate. These considerations notwithstanding, in caring for most patients, clinicians can employ the recommendations confidently to reduce the risks of atherosclerotic cardiovascular disease (ASCVD) events.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Clinical Algorithm

Mobile Device Resources

Patient Resources

Pocket Guide/Reference Cards

Resources

Slide Presentation

Staff Training/Competency Material

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Categories

IOM Care Need

Getting Better

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Safety

Identifying Information and Availability

Bibliographic Source(s)

Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC Jr, Watson K, Wilson PW. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014 Jul 1;63(25 Pt B):2889-934. [144 references] [PubMed](#)

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2014 Jul 1

Guideline Developer(s)

American College of Cardiology Foundation - Medical Specialty Society

American Heart Association - Professional Association

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Guideline Committee

Blood Cholesterol Expert Panel (originally convened as the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults [Adult Treatment Panel IV])

American College of Cardiology/American Heart Association Task Force on Practice Guidelines

Subcommittee on Prevention Guidelines

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Financial Disclosures/Conflicts of Interest

In consultation with the National Heart, Lung and Blood Institute (NHLBI), the policies adopted by the writing panels to manage relationships of authors with industry and other entities (RWI) are outlined in the methods section of each panel report. These policies were in effect when this effort began in 2008 and throughout the writing process and voting on recommendations, until the process was transferred to American College of Cardiology/American Heart Association (ACC/AHA) in 2013. In the interest of transparency, the ACC/AHA requested that panel authors resubmit RWI disclosures as of July 2013. Relationships relevant to this guideline are disclosed in Appendix 1 of the original guideline document. None of the ACC/AHA expert reviewers had relevant RWI (see Appendix 2 in the original guideline document).

Expert panel members having RWI or other possible conflicts of interest (COI) were allowed to participate in discussions leading up to voting as long as they declared their relationships, but they recused themselves from voting on any issue relating to their RWI or potential COI.

Guideline Endorser(s)

American Academy of Physician Assistants - Professional Association

American Association of Cardiovascular and Pulmonary Rehabilitation - Medical Specialty Society

American Pharmacists Association - Professional Association

American Society for Preventive Cardiology - Medical Specialty Society

Association of Black Cardiologists - Medical Specialty Society

Preventive Cardiovascular Nurses Association - Medical Specialty Society

WomenHeart: The National Coalition for Women with Heart Disease - Nonprofit Organization

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: Available from the [Journal of the American College of Cardiology \(ACC\) Web site](#) and from the [Circulation Web site](#) .

Print copies: Available from the ACC, 2400 N Street NW, Washington DC, 20037; (800) 253-4636 (US only).

Availability of Companion Documents

The following are available:

- Cholesterol Expert Panel. Managing blood cholesterol in adults. Systematic evidence review from the Cholesterol Expert Panel. Bethesda (MD): National Heart, Lung and Blood Institute (NHLBI); 2013. 239 p. Electronic copies: Available from the [National Heart, Lung and Blood Institute \(NHLBI\) Web site](#) .
- 2013 report on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease in adults: full panel report supplement. 2013. 396 p. Electronic copies: Available from the [Journal of the American College of Cardiology Web site](#) .
- 10 points to remember. Available from the [American College of Cardiology \(ACC\) Web site](#) . Also available as a video from the [ACC Web site](#) .
- 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults. Slide set. 2013. 82 p. Electronic copies: Available from the [ACC Web site](#) .
- 2013 prevention guideline case vignettes. Available from the [ACC Web site](#) .
- Methodology manual and policies from the ACCF/AHA Task Force on Practice Guidelines. 2010 Jun. 88 p. American College of Cardiology Foundation and American Heart Association, Inc. Electronic copies: Available from the [ACC Web site](#) .

A pocket guideline is available from the [Guideline Central Web site](#) . The 2013 Prevention Guidelines ASCVD Risk Estimator is available as a mobile app or in a web version from the [ACC Web site](#) .

Print copies: Available from the ACC, 2400 N Street NW, Washington DC, 20037; (800) 253-4636 (US only).

Patient Resources

The following is available:

- Guideline for treating blood cholesterol to reduce cardiovascular risk. Patient resource. Available from the [American College of Cardiology Web site](#) .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This NGC summary was completed by ECRI Institute on October 3, 2014. The information was verified by the guideline developer on January 23, 2015.

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